

J Orthop Sci (2015) 20:958–966
DOI 10.1007/s00776-015-0753-1

INSTRUCTIONAL LECTURE

Burdensome problems of chronic musculoskeletal pain and future prospects

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Received: 19 December 2014 / Accepted: 13 July 2015 / Published online: 11 August 2015

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Abstract According to a recent survey, about 15 % of the Japanese population suffers from moderate-severe chronic musculoskeletal pain persisting for at least 6 months. Social factors and related psychological factors (including depression) thus appear to greatly affect chronic musculoskeletal pain. This suggests the need for measures that take these factors into account. Treatment for musculoskeletal pain at present is generally based on a biomedical model that has been used for many years in this field, and modern medical imaging technologies have been a high priority to support this model and treatment strategy. Under the concept of the biomedical model, nonsteroidal antiinflammatory drugs, channel blockers and opioid analgesics are generally used as pharmacotherapy to alleviate chronic pain. However, these drugs are commonly associated with problems such as adverse effects, drug dependency and drug abuse, and they must be used with care. Surgery may also be effective in treating certain diseases, but studies have shown that many patients suffer residual chronic pain even after such treatment. Besides, exercise therapy has been found to be effective in treating many different types of chronic pain. Lately, various countries have been launching interdisciplinary pain centers that use a multidisciplinary approach to

treat chronic musculoskeletal pain. Treatment in these centers is provided by a team of specialists in anesthesiology, psychiatry and orthopedics as well as the relevant paramedical professionals. The therapeutic strategy is based on a cognitive-behavioral approach, and patients are taught about methods for restoring physical function and coping with pain, mostly with drugs and exercise therapy, so that any pain present does not impair function and the patient can reintegrate into society.

Introduction

A large majority of patients visiting hospitals for physical ailments are there because of bodily pain. Such complaints commonly involve musculoskeletal pain, such as in the limbs, neck and lower back. Most such patients visit orthopedic clinics in Japan. The large number of individuals suffering from musculoskeletal pain means that orthopedic clinics bear a large social responsibility. The therapeutic strategies used in orthopedic clinics begin with a diagnosis based on physical and radiological findings, but many issues exist at present. In particular, for patients who have suffered long-term chronic pain, an approach based on the conventional biochemical model often does not lead to relief of symptoms. The Japanese Ministry of Health, Labor and Welfare thus published a proposal in 2010 from a “Study Panel on Chronic Pain” that laid out a future approach for the medical treatment of pain (<http://www.mhlw.go.jp/stf/houdou/2r9852000000ro8f.html>). We herein review epidemiological studies conducted in Japan, such as studies of the prevalence of musculoskeletal pain, as well as biopsychosocial issues in the diagnosis and treatment of musculoskeletal pain. We also discuss future prospects for the treatment of musculoskeletal pain.

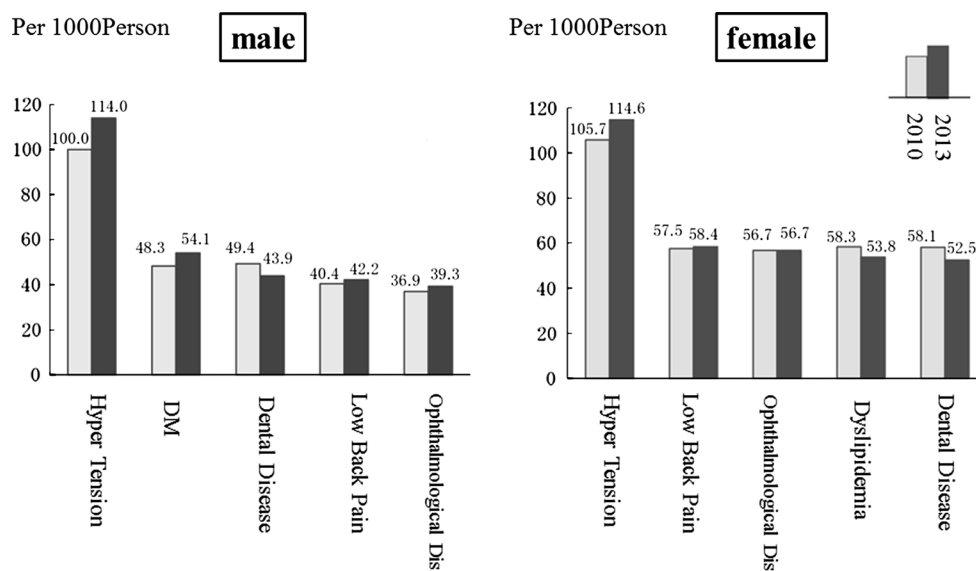
This instructional lecture was presented at the 87th Annual Meeting of the Japanese Orthopaedic Association, Kobe, 25 May 2014.

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Fig. 1 Top five patient care diseases from a comprehensive survey of living conditions conducted in Japan (2013/2010). Low back pain ranks fourth highest in males and second highest in females



Epidemiology of musculoskeletal pain in Japan

While details such as the strength and disease duration associated with the type of pain examined vary with survey methods, the population with musculoskeletal pain also differs between studies. In the comprehensive survey of living conditions conducted in Japan, low back pain, shoulder stiffness and joint pain always rank the highest in every age group for complaints by the public. Among males, low back pain is the most common complaint in all age groups starting with those in their 30s, and the prevalence of such complaints tends to increase with age. In comparison, shoulder stiffness is the most common complaint of females in their 20s–50s, and low back pain is the most common complaint from their 70s on. At the same time, the number of complaints of limb joint pain increases with age. Numbness is commonly seen in clinical settings of musculoskeletal ailments and tends to increase with age for individuals, but numbness alone does not greatly interfere with daily routines, while the presence of pain does [1].

A survey of the underlying illnesses that bring patients to the hospital showed treatment for low back pain as the fourth greatest problem among males and the second greatest among females (Fig. 1).

According to the 2010 comprehensive survey of living conditions, a survey of the factors leading to the need for assistance or nursing care determined that musculoskeletal disorders are the top ranking at 22.9 %, with falls or fractures accounting for 10.2 % and joints disease for 10.9 %. These findings show that musculoskeletal pain is not only highly prevalent in the population, but also a significant healthcare economics concern for Japan as a country that is already in the midst of an economic crisis and a challenge that the national government must address. In response, the

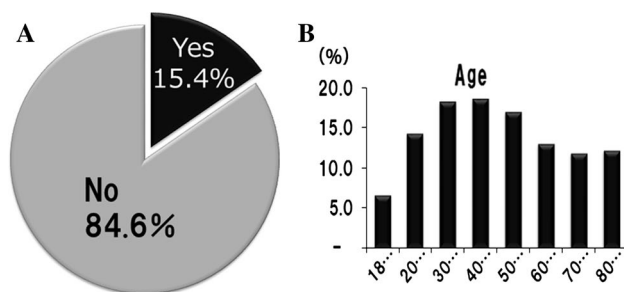


Fig. 2 Prevalence of musculoskeletal chronic pain in Japan; 15.4 % of the population experienced musculoskeletal pain persisting for at least 6 months (a). The prevalence of such pain is high among those in their 30s–50s (an age group comprising the key productive years; b). (From Nakamura M. et al. J Orthop Sci 2011;16:424–32)

Ministry's study panel on chronic pain formed a research group that has been conducting research to investigate the current state of chronic musculoskeletal pain and intractable pain. This research group has been undertaking detailed surveys on chronic musculoskeletal pain since 2010.

Nakamura et al. administered questionnaires to about 10,000 people in Japan [2] and reported that 15.4 % of the population experienced musculoskeletal pain persisting for at least 6 months (Fig. 2a), that the prevalence of such pain is high among those in their 30s–50s (an age group comprising the key productive years; Fig. 2b), that the prevalence of chronic pain is higher in large urban areas than in rural districts (Fig. 3) and that the frequency of chronic pain affecting the lower back, shoulders, neck and knees is high. Other findings from that survey were that the prevalence of pain was higher among office workers and professionals than among those working in primary industries such as forestry or fishery cooperatives, that there were

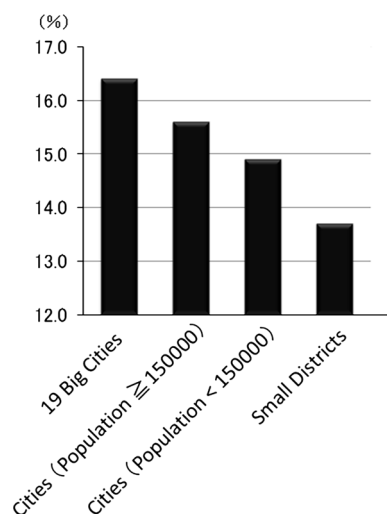


Fig. 3 City size and chronic musculoskeletal pain in Japan. The prevalence of chronic pain is higher in large urban areas than in rural districts. (From Nakamura, M. et al. *J Orthop Sci* 2011; 16: 424–32)

similar numbers of individuals visiting hospitals and clinics as those visiting folk remedy (acupuncture, massage, etc.) medical services for musculoskeletal pain treatment (about 20 % for each), that a large majority of individuals in pain were not receiving treatment at a clinic or hospital, and that about half of patients switched hospitals/clinics during treatment.

Concerning another aspect of chronic musculoskeletal pain, many cases are strongly related to degenerative diseases that accompany aging such as osteoarthritis. Indeed, it has been pointed out that there is a larger population of older people in pain in mountain village areas than in urban areas [3].

Besides, psychosocial backgrounds are known to affect the development and maintenance of musculoskeletal pain chronicity. An epidemiological survey called the Hisayama study examined the psychosocial background behind musculoskeletal pain and demonstrated that individuals with chronic low back pain often suffer depression and/or anxiety, with a particularly high prevalence of chronic pain among those with a tendency to alexithymia (i.e., an inability to identify their emotions; Fig. 4) [4]. In a survey we conducted in Owariasahi City, we found a high prevalence of chronic pain among those living alone (Table 1) [5]. Interestingly, people living alone showed a high score on the Kessler Psychological Distress Scale (K6) and a low score on the EQ-5D, suggesting this factor may be influential in the development and maintenance of chronic pain conditions.

Overall, these results suggest that the social background (super-aged society, nuclear family, working environment, etc.) and its associated psychological factors may affect the

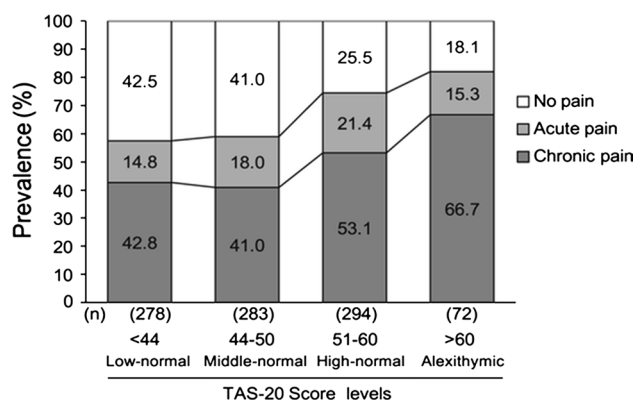


Fig. 4 Self-reported pain prevalence according to the Toronto Alexithymia Scale (TAS-20) score levels in a general population from the Hisayama Study health survey. Acute pain: <6 months of pain. Chronic pain: pain that experienced for 6 months or longer. (From Shibata M et al. *Plos One* 2014;9:e90984)

Table 1 Household size and chronic pain associate factors

Household size	Pain (NRS)	EQ-5D	K6	Chronic pain (%)
1	5.5	0.79	4.6	27
2 (with spouse)	5.1	0.85	2.5	18.2
2 (with parent)	4.6	0.85	4.2	11.8
2 (other pattern)	5.6	0.84	2.4	8.7
3	5.1	0.87	3.5	15.6

NRS Numerical Rating Scale, K6 Kessler Psychological Distress Scale

development of chronic musculoskeletal pain in addition to bodily dysfunctions.

Problems in the diagnosis, goal setting and treatment of musculoskeletal pain

The musculoskeletal system consists of the peripheral organs (muscle, joint, bone, vascular system, etc.) and sensory/motor/autonomic nervous systems (brain, spinal cord, peripheral nerve); complicated mechanisms underlie musculoskeletal pain. Therefore, it is essential to check and analyze the patients from many perspectives before the determination of the diagnosis/goal setting and therapeutic intervention.

Generally, analysis needs to clarify whether a specific patient's experience of pain carries a nociceptive component, neuropathic component or biomechanical problems (such as postural or alignment problems) and so forth. Psychosocial factors must also be considered in addition to the above if pain is not resolved and becomes prolonged (Fig. 5).

In addition, we have noted several concerns about making the diagnosis and treatment.

Fig. 5 Important diagnostic check points to analyze chronic pain conditions. To make a therapeutic program for chronic pain patients, it is necessary to check both the characteristics of pain and pain simultaneously

<u>Check Points</u>	
Characteristics of Patients	Characteristics of Pain
Patients background Family problem Working environment Cognitive Function (Dementia etc.) Medication HX Surgery HX Alcohol HX Gain(benefit) from Disease Worker's compensation Traffic accident Other	Nociceptive component Neuropathic Pain compo. Biomechanics

Problems

Biomedical model-based diagnosis

Diagnosing and specifying the pain source by simple biomedical examinations are generally not promising. For example, specific low back pain, which involves a certain pain source in the lumbar spine, may be caused by problems with the intervertebral discs, facet joints, nerve roots or muscles of the lower back. Diagnoses for pain in these areas are often based on radiological findings and physical examinations. However, statistics from the “Research on Osteoarthritis Against Disability” (ROAD) study determined that while X-rays confirm osteoarthritis in 30 million people, only about 10 million suffer pain, indicating a high rate of false-positive results from the perspective of using X-rays as a diagnostic tool for pain [6, 7]. Similarly, statistics on osteoarthritis as the most common cause of knee pain showed that only about one-third of patients identified radiographically as having the disease (about 8 million in Japan) actually suffer pain. An extremely large number of false-positive results is also seen with spinal MRI, in which evidence of epidural compression is present, but not associated with pain. Conversely, many patients experience pain but show unclear imaging findings.

The overseas literature on causes of chronic low back pain indicates that a cause can only be identified in about 15 % of cases even after various tests, and all other cases are classified as nonspecific low back pain [8]. In other words, the problem underlying low back pain is unlikely to be understood and linked to an actual diagnosis unless a diagnosis is made based on a detailed knowledge of patient background information, including physical findings such as posture, history of the pain, and work-related and environmental factors.

For these reasons, provocation tests and nerve blocks at pain sites are used for functional diagnosis [9]. Nevertheless, we have to mention that a strong placebo effect is known to be associated with these invasive trials/testings [10].

Typical psychosocial concerns that influence pain chronicity

When providing treatment, it is necessary to reaffirm that “pain” represents “an unpleasant sensory and emotional experience” registering in the brain.

Indeed, it is important to recognize that organic treatment approaches often prove unsuccessful in patients with chronic musculoskeletal pain who suffer an element of distorted perception of the pain in addition to those with cognitive impairment. The following problems should also be considered as potential contributors to prolonged pain:

- Effect of stigmatization: provision of a diagnosis or words implying a diagnosis may affect symptoms (for example, a diagnosis of a herniated disc based on imaging evidence may lead a patient to consider the hernia as the root of all of their symptoms);
- Incentivization of the illness (for example, worker's compensation or accident insurance benefits or if a pathology exists in the family); or
- An environment that causes patients to focus excessively on their pain or in which they have no other option but to do so.

Goal settings

Musculoskeletal pain commonly becomes chronic. However, it is often the case that not only functional, but also

numerous components, such as psychosocial issues, cause the pain to become prolonged. Before providing treatment, detailed examination of the clinical condition at the site of the pain is certainly essential, but analysis of the condition should also include observation of the patient from various perspectives, including their environment.

After assessing many aspects, the therapeutic goal should be considered not only from the perspective of pain intensity control, but also from the perspective of improving the ADL and QOL as a matter of primary importance.

General indications, usage and concerns of individual therapeutic approaches

Pharmacotherapy

Since many causes of musculoskeletal pain involve an inflammatory component, nonsteroidal antiinflammatory drugs (NSAIDs) are currently generally prescribed as first-line pharmacotherapies. However, recent research suggests that pharmacotherapies should take neural mechanisms into account, even in cases of acute trauma. Indeed, the pain signal transmitted to the spinal cord through primary afferents causes a dorsal root reflex that promotes the release of inflammatory neuropeptides from the peripheral nerves and triggers neurogenic tissue inflammation. Moreover, as many types of painful ailments such as low back pain become chronic, pain that is initially nociceptive may cause defensive muscle contractions or neuropathic pain. Accordingly, when prescribing drugs, it is necessary to consider inflammation and nociceptive pain, muscular components and nervous system components (including neuropathic pain) at the same time.

As analgesic medications (such as anxiolytics, antidepressants and anticonvulsants) have recently come into common use for treating pain (particularly neuropathic pain) in the field of orthopedics, we must consider the adverse effect of these medications since many orthopedic providers are not familiar with these drugs. In Japan, benzodiazepines are frequently used as anxiolytics over the long term, but the Food and Drug Administration (FDA) in the USA does not recommend these agents for long-term use because of the development of resistance to the effects, the risk of drug dependency and the occurrence of withdrawal symptoms when taking the patient off these drugs. Anticonvulsants suppress the transmission of pain signals by blocking neural excitation and neurotransmitter release. However, they may also trigger numerous side effects, such as drowsiness and dizziness, because of their actions in ion channels (sodium channels, calcium channels, etc.) distributed throughout the nervous system. It is particularly important to note that elderly patients or patients with spinal cord disorders who may have reduced functioning

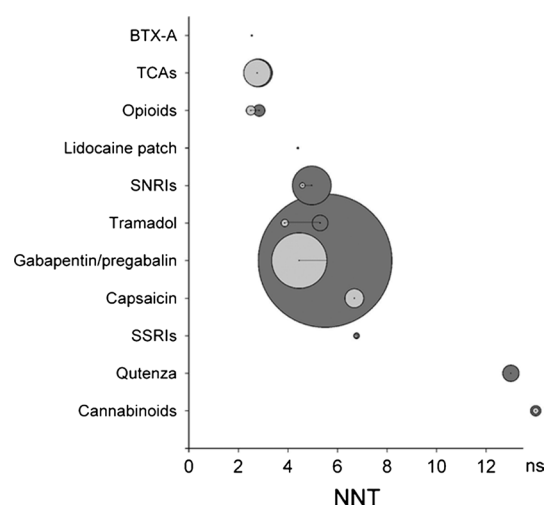


Fig. 6 The number needed to treat (NNT) with analgesic drugs for neuropathic pain. Numbers needed to treat (NNT) values for various drug classes in all central and peripheral neuropathic pain conditions. BTX-A botulinum toxin type A; TCAs tricyclic antidepressants; SNRIs serotonin noradrenaline reuptake inhibitors; SSRIs selective serotonin reuptake inhibitor. The figure illustrates the change from 2005 values in light gray to 2010 values in dark gray. The circle sizes indicate the relative number of patients who received active treatment drugs in trials for which dichotomous data were available. [From Finnerup et al. Pain 150(3) pp 573–581]

in the nervous system may be at a higher risk of falls than usual and should take extra care when using these drugs. Opioids have also come into use for treating musculoskeletal pain. In addition to the unique side effects of opioids such as nausea, opioids have been noted for associations with drug resistance and dependency as well as social problems such as drug abuse in other countries. Medical providers must become well versed in the use of these drugs and only prescribe them to patients who are indicated while closely monitoring the dosage. While the appropriate use of pharmacotherapies can benefit patients, drug effects are often limited and the number needed to treat (NNT; the number of patients who must be treated for 1 patient to achieve high efficacy against their pain, i.e., reducing pain by half) in the treatment of neuropathic pain ranges from about 3 to 10 (Fig. 6) [11].

According to reports on evidence-based medicine to date, NSAIDs, intra-articular injection of hyaluronic acid and exercise therapy have been effective for osteoarthritis-associated joint pain, and the Osteoarthritis Society International has created guidelines [12]. A Japanese version has also been developed. However, many people do not see sufficient improvement with these conservative treatments and choose artificial joint replacement as an operative treatment.

Overall, it is therefore important to remember that few patients achieve complete relief from pain using

pharmacotherapy alone. The musculoskeletal system comprises organs that maintain their performance through movement, and care should be taken to avoid overprescribing drugs.

Physiotherapy

Manual physiotherapy, thermotherapy and traction therapy have been used for many years, and while these options do offer temporary relief from muscle pain, few patients achieve complete remission. Meta-analysis of exercise therapy has been reported to reduce pain and improve functioning in those with chronic pain (lasting at least 12 weeks) and to be equally effective to no treatment or conservative treatment in those with acute pain (lasting up to 6 weeks) [13]. A summary of systematic reviews from countries outside Japan showed exercise therapy to be effective for treating a wide range of ailments, including chronic low back pain [14]. When applying a physiotherapy or exercise therapy approach, methods in which the patient only passively receives treatment may have only temporary effects. Instructing patients on how to perform the treatment themselves may be necessary, even if doing so does not offer complete relief from pain.

Surgical treatment

Surgical/operative treatment has the potential to significantly alleviate symptoms, for example by decompression of the affected nerves or with artificial joints and other types of reconstructive surgery in the musculoskeletal systems. It is important, however, to remember that operative techniques in invasive treatment have their own limitations, and this approach is not infallible.

Surgery on the lumbar spine is performed to relieve compression of nerve roots or the cauda equina caused by a narrow canal or herniated disc to alleviate neuralgia. During surgery, multifidus muscle retraction and separation of perineural tissues in the spinal canal need to be performed, but the former may result in denervation of the multifidus muscle, and the latter may result in perineural adhesions (e.g., epidural adhesions), among other serious consequences [15]. Postoperatively, patients may experience loss of muscle strength in the back or fatigability, which may be accompanied by varying degrees of low back pain or adhesive pain and numbness. Indeed, in one randomized controlled trial (RCT), operative treatment showed better outcomes on clinical presentation than conservative treatment in the long term, but the difference between the two decreased after 10 years [16]. In another RCT on patients with pain lasting several weeks, no long-term differences in outcome were seen between patients who continued conservative treatment and those who underwent early surgery [17, 18]. These findings have been incorporated into the

guidelines of the Japanese Orthopedic Associations. However, attention must be paid to new treatments for lumbar disc diseases, such as condoliase treatment, which are continuing to be developed.

Appropriate indications for surgery for low back pain in Japan are generally fractures (compression fracture, spondylolysis, etc.) and pathologies resulting from nerve compression. Concerning about spondylolysis, the incidence of lumbar spondylolysis in the Japanese general population was 5.9 % [19]. However, it should be noted that many of them are asymptomatic.

Pain from such problems as nonunion of a spinal compression fracture has recently been treated with vertebroplasty [20, 21] or kyphoplasty [22] as surgical approaches to treat individuals with chronic back pain. However, these procedures are generally for older adults with bone loss. Moreover, these interventions carry their own risks and may lead to new problems after surgery, such as new fractures. From the perspective of preventive care, new treatment methods are needed.

Concerning joint surgery, the number of artificial joint procedures in Japan is growing dramatically since many people do not see sufficient improvement with these conservative treatments. Including those with osteoarthritis of the hip or knee, as many as 100,000 people a year are choosing joint replacement surgery. Artificial joints are currently used as a final resort, but generally cannot achieve the range of movement required for activities of the Japanese lifestyle, such as kneeling. Moreover, a study from outside Japan showed that 8–23 % of patients still experience residual pain after receiving an artificial joint [23], indicating that many challenges remain.

Cognitive behavioral therapy and multidisciplinary approaches

Generally, a biomedical approach is utilized to clarify the cause of musculoskeletal pain and to use drugs and/or surgery to remove or alleviate the problem. However, pain is not an entirely biological issue and has many components, including social and psychological aspects. These components are almost always tightly interwoven in patients with refractory pain. Remembering the role these factors may play when treating patients with musculoskeletal pain is therefore important. For patients who are strongly engulfed in their pain psychologically, treatment should not focus solely on removing the pain, but instead should also treat their psychological and social difficulties with the aim of improving activities of daily living (ADL) and quality of life (QOL). This approach is based on the biopsychosocial model, which stresses the consideration of psychological factors and social factors as equally important to biological factors in patients with pain. This approach employs

Fig. 7 Pain virtuous cycle. Patients can leave the non-virtuous cycle by learning how to improve their body function and understand chronic pain problems

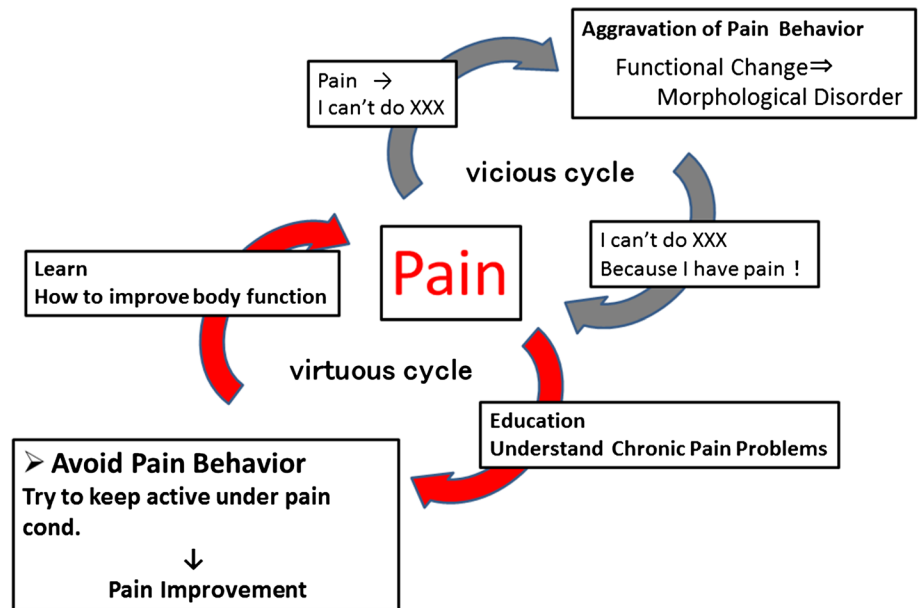
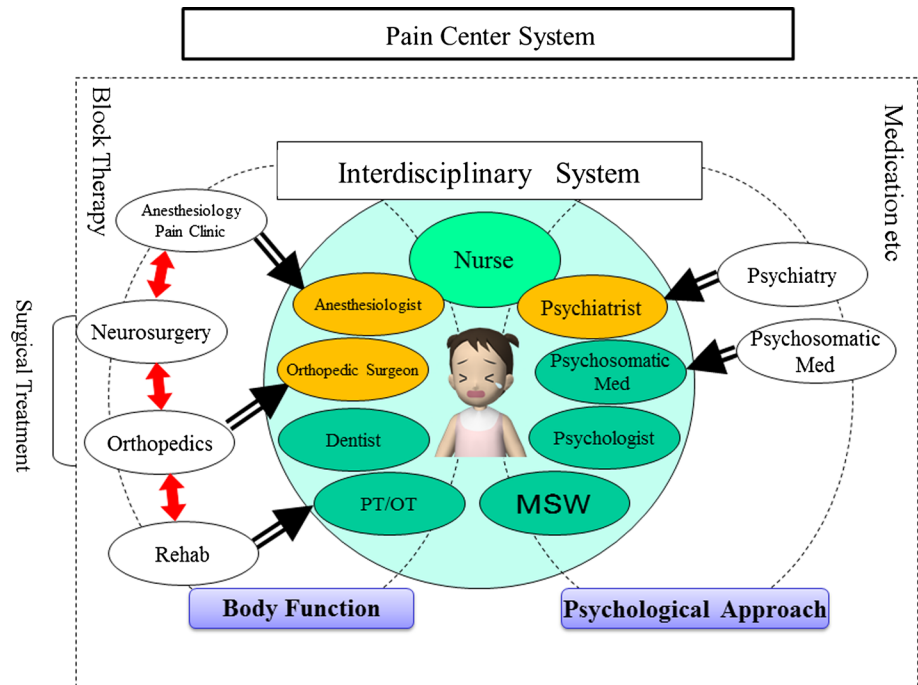


Fig. 8 Principle of the interdisciplinary pain center system. An interdisciplinary pain center is a single unit-based system for carrying out multidisciplinary pain management. The center has a broad range of clinical staff, patient care services, pain conditions treated, and educational and research activities



cognitive-behavioral therapy, which is based on operant conditioning to reduce painful behaviors and enable the patient to coexist with the pain [24].

Specifically, this approach involves changing the patient's thinking and behavior patterns from "I cannot do XXX because I feel pain" to "I can do XXX despite the pain." This can both improve the ADL and QOL and create conditions under which the patients are not overwhelmed by their experience of pain (Fig. 7).

In addition to specialists in orthopedics, anesthesiology and other fields who treat functional disorders, it is important to use a multidisciplinary approach, including psychiatrists, clinical psychologists and others specializing in psychiatry/psychology to set patients along a more positive path (Fig. 8). The role of the co-medical team together with the doctor is important. For example, a nurse, with a point of view that is different from the doctor, carries out the psychological support of patients and their families. In

addition, physical therapists work toward the functional improvement of the body. Clinical psychologists analyze the background of the patient and perform psychotherapeutic interventions.

Numerous interdisciplinary pain centers that act as single units with all these functions have been founded in various countries [25]. As these centers have achieved excellent treatment outcomes with various new attempts, such as group treatment, we have experimentally tried this approach at our own institution and have achieved definite improvements with this design, even in refractory cases [26].

Conclusion

Musculoskeletal pain commonly becomes chronic. However, it is often the case that not only functional, but also numerous components such as psychosocial issues cause the pain to become prolonged. When providing treatment, detailed examination of the clinical condition at the site of the pain is certainly essential, but analysis of the condition should also include observation of the patient from various perspectives, including their environment. As all sorts of new treatments continue to be developed with the progress of medical care, each new treatment modality will inevitably show some form of disadvantage, and the problems mentioned above must be considered to ensure the provision of treatment that not only aims at controlling pain, but also considers the widespread improvement of the ADL and QOL as a matter of primary importance.

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